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MDM2 N-TERMINAL DOMAIN FLEXIBILITY MODELING

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The development of MDM2-p53 protein-protein interaction inhibitors is one of the current trends in anti-cancer drug design since MDM2 blocks the proapoptotic activity of the p53 protein and prevent tumor cell death. Understanding of the interaction mechanism and sructural features of binding sites of these proteins allows rational design of such inhibitors [1].

The traditional approach is based on the mimicking of the p53 protein alpha-helix binding to MDM2. It is assumed as the three-point protein-inhibitor binding within the hydrophobic cavity of MDM2 formed by 18-120 amino acids of the protein. However, this approach does not consider the involvment of the flexible fragment formed by the first amino acids of MDM2.

To date, several models of the MDM2 protein with full-length N-terminal domain are presented in Protein Data Bank, so it is possible to analyze the behavior of the flexible protein fragment when interacting with a potential inhibitor.

Here we analyzed the dynamics of the MDM2 protein complex with a small molecule MDM2 inhibitor when passing from open to closed conformation of the N-terminal domain of MDM2. 1Z1M model from Protein Data Bank [2] was used as the initial state of MDM2; it represents the open conformation of the MDM2 N-terminal domain.

The molecular dynamics simulation performed for MDM2 without a small molecule ligand showed a monotonic increase in the energy of the fixed states during the formation of the closed conformation, which indicates the preferred existence of the open form of the protein. The molecular dynamics study of the MDM2 complex with a highly active protein-protein interaction inhibitor showed a monotonic decrease in the energy of the fixed states during the formation of the closed conformation.

The obtained data indicate that the interaction with the inhibitor stabilizes the structure of the N-terminal domain and promotes the formation of the closed conformation of the MDM2 protein, which prevents the binding and deactivation of the anti-oncogenic protein p53.

Thus, in order to develop effective MDM2 inhibitors one should consider the ability of candidates to interact with the flexible MDM2 fragment and to provoke the formation of the closed protein conformation.

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2. Uhrinova S. et al. *J. Mol. Biol*, 2005, **350**: 587-598.

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